

Cytomegalovirus prevalence in pregnant women: the influence of parity

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Abstract

Over 20 000 women attending for antenatal care at three London hospitals were prospectively studied to determine the prevalence of cytomegalovirus (CMV) antibodies; 54.4% of these women were CMV seropositive. Ethnic group was strongly associated with CMV status: 45.9% of white women were seropositive, 88.2% of Asian, and 77.2% of black women (African/Caribbean ethnic origin). Among 12 159 white women born in the British Isles, seropositivity was independently associated with increasing parity, older age, lower social class, and being single at antenatal booking. The findings are consistent with the hypothesis that, in the UK, child to mother transmission of infection plays a significant part in the acquisition of CMV infection in adult life.

Cytomegalovirus (CMV) is common worldwide and a well recognised cause of handicap in infants born with congenital infection. The majority of congenitally infected infants develop normally, but about 10% are likely to have permanent CMV related damage, ranging from unilateral sensorineural hearing loss to multiple disabilities which can include microcephaly, cerebral palsy, sensorineural hearing loss, impaired vision, and mental retardation.¹

Congenital infection can follow either primary or recurrent maternal infection, but the likelihood of fetal infection and the risk of associated damage is higher after a primary infection.^{2 3} In developing countries, where most people acquire CMV infection in early childhood, most congenital infections follow maternal recurrent infection. In the UK, although acquisition of CMV infection in infancy is common (largely attributable to transmission from seropositive mothers at delivery or through breast feeding⁴), more than 60% of women reach adult life still susceptible to CMV and about three quarters of congenital infections are likely to be attributable to primary maternal infection.⁵

Sexual transmission is acknowledged to play an important part in the acquisition of CMV infection in adult life.^{6 7} Studies in the USA examining the transmission of CMV in day nurseries have suggested that children may also be an important source of infection for their mothers or other caretakers.^{8 9} The relative importance of contact with children in comparison with other modes of transmission of infection in adult life is unclear and will

depend on a number of factors relating to breastfeeding, sexual and child rearing practices, which vary considerably between countries and social and ethnic groups. The relative importance of different modes of transmission of CMV in the UK is unknown, although there is some anxiety about the possibility of occupational risk for women working with young children.¹⁰

The present analysis is based on data collected as part of a large prospective study of CMV infection in pregnancy carried out in west London between 1980 and 1986. The main aims of the study were to examine the CMV serological status of women booking for antenatal care, estimate the incidence of congenital CMV infection, and investigate its long term sequelae.³ This paper explores the independent effects of social class, marital status, age, and parity on maternal seroprevalence at antenatal booking.

Subjects and methods

All women booking for antenatal care at three west London hospitals were eligible for enrolment in the study, which continued for one year at the first hospital, two years at the second, and six and a half years at the third. Details of maternal age, parity, marital status, country of birth, race, and both maternal and paternal occupation were collected by interview at the first antenatal appointment, together with a blood sample to establish CMV serological status. Sera were tested for CMV antibodies by complement fixation, and detection of specific antibody at a dilution of 1:10 was taken to indicate past CMV infection. While this assay may be less sensitive than others now available, it is acceptable for epidemiological purposes; any slight inaccuracy in the overall estimation of seroprevalence will not affect the internal comparison of results presented here.

Analysis of the whole dataset was carried out using SAS.¹¹ A grouped binomial relative risk regression¹² was performed on a subset of the data, white women born in the British Isles, to explore the independent roles of parity, marital status, social class, and age.

Women were assigned to five parity groups, ranging from those who had no previous children to those who had four or more. Two marital status groups were defined: one comprising women who were married or cohabiting at the time they booked for antenatal care, and the second those who were single, divorced, widowed, or separated (hereafter referred to as

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single). Social class was categorised by partner's occupation for married and cohabiting women, and by their own occupation for single women,¹³ and was then divided into four occupational groups: professional (Registrar General's social class I and II), clerical (III non-manual), manual (III manual, IV, and V), and unclassified (unemployed, students, housewives, and armed forces). Finally, the mean age of each subgroup of women was calculated and used as the age value of that subgroup in the regression.

Results

Altogether 21882 women who booked consecutively for antenatal care were enrolled into the study. Many of these women booked for more than one pregnancy during the study period, but only the first pregnancy in which a blood sample was collected was included in this analysis; the CMV serological status of 20 684 women (94.5%) was known.

The overall CMV seroprevalence was 54.4%, but the study population was ethnically diverse and ethnic group was strongly associated with seroprevalence, Asian women having the highest level, 88.2%, and white women the lowest, 45.9% (table 1). There were marked differences in both seroprevalence and demographic characteristics between women of the same ethnic group who were born in different countries. In addition, British born women of all ethnic groups were less likely to be seropositive than those born elsewhere, and also tended to be younger and more often single. It is likely that family structure and organisation, and arrangements for the care of young children, also varied between the different groups.

The complex relationship of age, parity, social class, marital status, and CMV seroprevalence was therefore explored in the homogeneous subgroup of this London population, the 12 559 white women born in the British Isles. The overall CMV seroprevalence in this subgroup was 42.8%. As shown in table 2, there was a clear trend of rising seroprevalence with increasing age from 36.6% in those under 20 years to 51.4% in women aged 35 and over, and with increasing parity from 38.9% in nulliparous women to 66.2% in women expecting their fifth or subsequent child. Single women were more likely to be seropositive than those with a partner, and the lower the social class the higher the proportion of seropositive women.

The figure shows the CMV seroprevalence by age and parity. While there was a steady and gradual rise in seropositivity with age for

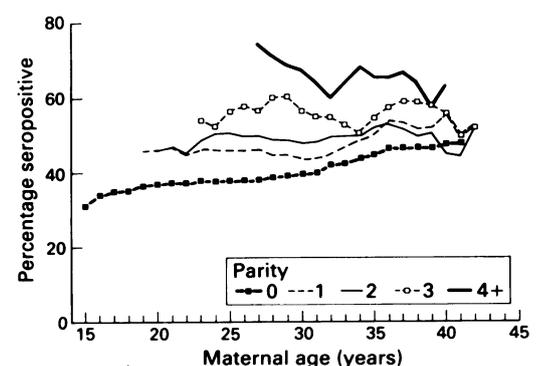
Table 2 CMV seroprevalence and age group, parity, marital status, and social class in 12 559 white women born in the British Isles

	Seropositive (%)	95% Confidence interval (%)
Overall	42.8	41.9 to 43.7
Age group (years):		
<20	36.6	33.6 to 39.7
20-24	39.8	37.9 to 41.7
25-29	41.7	40.2 to 43.2
30-34	44.5	42.8 to 46.0
35+	51.4	48.8 to 54.1
Parity group:		
0	38.9	37.8 to 40.0
1	46.4	44.7 to 48.1
2	49.5	46.7 to 52.4
3	55.4	50.3 to 60.5
4+	66.2	58.9 to 73.6
Marital status:		
Single	46.9	44.8 to 49.0
Married/cohabiting	41.9	40.9 to 42.9
Social class:		
Professional	40.0	38.7 to 41.4
Clerical	43.5	41.3 to 45.6
Manual	45.2	43.6 to 46.9
Unclassified	45.5	43.1 to 47.9

nulliparous women, this was not the case for parous women. The more children a woman already had, the higher the probability of being seropositive, and the smaller the effect of increasing age. Indeed, younger women of high parity were more likely to be seropositive than older women. This suggests that there is a particularly high rate of acquisition of CMV infection in young parous women.

To estimate the independent effects and thus the relative importance of age, parity, marital status, and social class, a binomial relative risk regression was carried out on the 12 159 (96.8%) members of the subgroup for whom all the variables of interest were available.

Two models were fitted: in the first, all four variables were categorical; and in the second, social class and marital status were categorical, and age and parity continuous. The first model accounted for slightly more of the variance than the second, but the difference between the two was not significant at the 5% level; the second model was therefore used so that age and parity effects could be estimated per year of age and per previous child born. The possibility that there might be interaction between the factors was explored. The only statistically significant interaction was that between age and parity, with parity having a greater effect on seroprevalence in younger



Seroprevalence of CMV in 12 559 white women born in the British Isles and attending for antenatal care in west London 1980-6 (five year rolling averages).

Table 1 Ethnic group and CMV seroprevalence

Ethnic group (No in group)	Seroprevalence (%)	95% Confidence interval (%)
Asian (1939)	88.2	86.8 to 89.7
Black (1972)	77.2	75.3 to 79.0
Oriental (533)	83.9	80.7 to 87.0
White (15 586)	45.9	45.1 to 46.7
Other (157)	58.0	50.2 to 65.7
All women (20 684)	54.4	53.6 to 55.0

Table 3 Logistic regression for 12 159 white women born in the British Isles, showing log likelihood χ^2 tests and estimated relative risks

	χ^2	df	Relative risk	95% Confidence interval
Age (per 5 years)	68.1*	1	1.117	1.09 to 1.15
Parity (per baby)	70.9*	1	1.140	1.11 to 1.18
Social class:	35.3*	3		
Professional			1	
Clerical			1.102	1.04 to 1.17
Manual			1.166	1.11 to 1.23
Unclassified			1.128	1.05 to 1.21
Marital status:	45.9*	1		
Married/cohabiting			1	
Single			1.233	1.17 to 1.30
Age (per 5 years, per baby)	9.3**	1	0.973	0.96 to 0.99

Baseline CMV seroprevalence 33.05% (95% confidence interval 31.6% to 34.5%) (nulliparous, age 25, married, professional social class).

*Extra deviance to remove from model with main effects only.

**Extra deviance to add to main effects model.

women than in older women; this term was therefore added to the model.

Table 3 shows the χ^2 value, relative risk for seropositivity for each factor, and its 95% confidence interval; the χ^2 value tests the statistical significance of each factor when the others are held constant. Age and parity were most strongly associated with seroprevalence, followed by marital status, and then social class.

The risk of being seropositive increases with each successive child. A 25 year old woman having her second child is an estimated 1.14 times more likely than a nulliparous woman of the same age to be seropositive, if she is having a third child this increases to 1.3 (1.14²) and for her fourth to 1.48 (1.14³). Because of the negative interaction between age and parity, the increased risk associated with higher parity is less in older women. For a woman aged 35, the corresponding figures relative to a nulliparous woman aged 35 are 1.08, 1.16 and 1.26 (for instance the latter is 1.14³ × (0.973²)³).

This can be compared with the relative risks for the other factors: a 30 year old nulliparous woman is estimated to be 1.12 times more likely to be seropositive than a 25 year old nulliparous woman of the same marital status and social class; a woman who works (or whose partner works) in a manual occupation is 1.17 times more likely than a professional woman to be seropositive; a single woman is 1.23 times more likely than a married or cohabiting woman to be seropositive. The relative risks combine multiplicatively, so a single 25 year old woman with one child is 1.41 (1.14 × 1.233) times more likely than a nulliparous married 25 year old of the same social class to be seropositive.

Discussion

The epidemiology of CMV in a particular population, and the relative importance of different modes of transmission, are likely to be determined by cultural practices relating to breast feeding,^{4 14} child rearing, child care arrangements,¹⁵ and sexual behaviour.^{6 16-18}

Ethnic group was an important determinant of CMV seroprevalence in this London population. Women who were born in countries where CMV seroprevalence is high at young ages (for instance, parts of Africa,¹⁹ South

America,²⁰ Asia,²¹ and southern Europe^{22 23}) had rates of seroprevalence which probably reflected their acquisition of infection in infancy and childhood. Similar observations have been made in other studies carried out among ethnically diverse populations.²⁴⁻²⁷

In order to explore the independent effects of social class, marital status, age, and parity, a restricted analysis was undertaken of the factors associated with seropositivity in a homogeneous subgroup with a high proportion of women susceptible to primary CMV infection during their childbearing years: approximately 12 500 white British born women. Each of the four factors, parity, age, social class, and marital status, had a strong independent association with CMV seroprevalence.

The independent association of parity with seroprevalence, having controlled for the other factors, was particularly striking. In all age groups women of higher parity were more likely to be seropositive than those having their first or second child.

This effect of parity among women of the same age could be accounted for by child to mother transmission of infection, from children who had themselves acquired infection from elsewhere. A number of nursery studies have documented child to child transmission of infection, and examples of children and nursery staff sharing the same virus strain have been identified.²⁸⁻³⁰ Studies in the USA have found high rates of seroconversion among some day care workers,³¹⁻³³ and children who acquire infection in day nurseries have been shown to transmit infection to their susceptible mothers,¹⁵ as have infants who were infected through blood transfusion.⁸

Several other studies have observed an association between parity and CMV status. A longitudinal study in a middle class population in Houston, USA,³⁴ found that the presence of young children in the home was a risk factor for primary infection in pregnancy, and that maternal seropositivity was associated with the presence of older children.²⁶ The Alabama group also observed a rising seroconversion rate with subsequent pregnancies in a high socioeconomic group.³⁵

An alternative, or additional, explanation for the association of parity and seroprevalence could be that women who have had more pregnancies have also, on average, had more previous sexual partners. In an evaluation of the relationship between sexual practices and CMV seroprevalence among women in Seattle, USA,⁷ sexual activity was an important determinant of seropositivity, but the association was stronger for white than for black women, and in addition, parity was associated with seropositivity in the white but not in the black women.

Much of the crude effect of age on seroprevalence was accounted for by parity, but even after controlling for the other factors a major independent age effect remained. A relatively high incidence of primary infection in infancy is probably followed by a lower incidence through childhood, which increases in adolescence with the onset of sexual activity.

Tempting though it is to attribute the rise in seropositivity with increasing age to the acquisition of infection in adult life, this interpretation of cross sectional age specific seroprevalence data could be misleading. Different birth cohorts of women may have experienced different rates of acquisition of infection in infancy, adolescence, and adult life as a result of changing patterns of breast feeding and sexual activity.

Infants born to seropositive women may acquire CMV infection during delivery,^{36 37} or through breast feeding;¹⁴ currently approximately 20% of children born in Britain are likely to be seropositive by the age of 12 months.⁴ Virtually all women enrolled in this study were born between 1935 and 1970, a period which saw an appreciable decline in breast feeding. Until the 1930s most children were breast fed for several months, but by 1946 only 45% of British babies were still breast fed at the age of 2 months,³⁸ and by 1970 this had declined to only 30% at the end of the first week.³⁹ CMV is more likely to be present in breast milk after the first week than before, and colostrum is a relatively poor source of virus.^{4 40} It is therefore likely that some of the apparent effect of increasing age in this population is related to lower levels of CMV infection in infancy in the younger women.

Age at first sexual intercourse, number of sexual partners, and the use of barrier methods of contraception have all been associated with CMV seroprevalence,⁷ and are also factors which are likely to show both a cohort effect and social class differences.

This analysis demonstrated an interaction between parity and age, in that the association of high parity with seropositivity was greater in younger women than in those who were older. Indeed, women who were pregnant with a fifth child by their mid to late 20s were more likely to be seropositive than older women of high parity, who had presumably either spaced their children out more, or started having them later.

Several studies have shown an association between seroprevalence and social class,^{35 41} and some studies of seroconversion in pregnancy have been restricted to higher socioeconomic groups in order to enrol a relatively high proportion of seronegative women. It is possible that single pregnant women have had, on average, a greater number of sexual partners than married or cohabiting pregnant women, and this could, to some extent, account for the association of single status with seropositivity. However, seroprevalence may be associated with child care arrangements, as discussed above, and use of day care is strongly influenced by both social class and marital status, as well as maternal age and most obviously parity. In most of the UK, and certainly in the London area from which the study population was drawn, access to day care facilities is highly dependent on family situation and socioeconomic status. Women of low socioeconomic status are more likely than professional women to have their children cared for in day nurseries; single women

and very young women, particularly those who have several children, are also more likely to use these facilities.

Conclusion

Within each age band and social class group, women with children are likely to differ from those without children, and it is difficult, using cross sectional data, to disentangle the effects of social and cohort factors, such as child care arrangements, breast feeding experience, and sexual history. None the less, in this study the independent effect of parity, having allowed for age, social class, and marital status, was very striking and certainly consistent with the hypothesis that children are an important source of infection for their susceptible mothers.

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